REPLENISH Trial: Endometrial Safety with a 17β-Estradiol and Progesterone Combination (TX-001HR) in Postmenopausal Women with Vasomotor Symptoms

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Introduction

- Hormone therapy for postmenopausal women with an intact uterus requires the addition of a progestogen to prevent endometrial hyperplasia and reduce the incidence of endometrial cancer[1]
- Use of compounded bio-identical hormone therapy (CBHT) has become highly prevalent in the US since the 2002 published report of the Women's Health Initiative[2]
  - An estimated 1 to 2.5 million US women use unapproved CBHT products,[2,3] representing up to 21 to 39 million prescriptions annually[2]
- Endometrial hyperplasia and endometrial cancer have been reported with CBHT use[4-6]
- TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17β-estradiol and progesterone (E2/P4; sometimes referred to as bio-identical hormones) in a single, oral softgel capsule developed to treat menopausal vasomotor symptoms (VMS) in women with an intact uterus
  - No similar combination HT product has been approved yet in the US or Europe

Objectives

- To evaluate the endometrial safety of four doses of TX-001HR in participants of the REPLENISH trial

Methods

Study Design and Population

- REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated various daily, oral doses of TX-001HR in postmenopausal women with an intact uterus (**Tables 1 and 2**)

Table 1. Key inclusion and exclusion criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Healthy postmenopausal women aged 40-65 years • Intact uterus • Body mass index ≤34 kg/m² • Vasomotor symptoms associated with menopause • Acceptable endometrial biopsy results	• History of endometrial hyperplasia, melanoma, or uterine/endometrial, breast, or ovarian cancer • History of thrombosis of deep veins/arteries or thromboembolic disorder, coronary artery or cerebrovascular disease, chronic liver or kidney dysfunction/disorder, malabsorption disorder, gallbladder dysfunction/disorders, diabetes, thyroid disease or any other endocrine disorder • Prior use of estrogen-, progestogen-, androgen-, SERM products within 1 week to 6 months depending on the formulation • Medications that are known to induce or affect estrogen and/or progestogen drug metabolism or activity (≤4 weeks)
VMS Substudy	
• ≥7/day or ≥50/week moderate-to-severe hot flushes	

Table 2. Treatments and randomization

Randomization	Treatment Groups*
• Women with moderate-to-severe hot flushes were randomized 1:1:1:1:1 to one of four E2/P4 doses or placebo (VMS substudy and endometrial study) • Women not qualifying for the VMS substudy were randomized 1:1:1:1 to one of four E2/P4 doses (endometrial study)	• 1.0 mg E2/100 mg P4 • 0.5 mg E2/100 mg P4 • 0.5 mg E2/50 mg P4 • 0.25 mg E2/50 mg P4 • Placebo

E2: estradiol; P4: progesterone.
*All women took 2 capsules in a double-blind, double dummy manner to maintain study blinding as 2 different capsule sizes were necessary to accommodate the different doses.

- All women completed daily diaries
  - Frequency and severity of their VMS through week 12
  - Bleeding and spotting through month 12
    - Bleeding was defined as requiring sanitary protection
    - Spotting was defined as not requiring sanitary protection

Endometrial Safety Endpoints

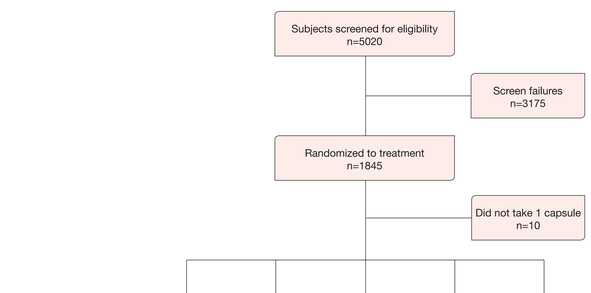
- The primary safety endpoint was the incidence of endometrial hyperplasia at month 12
  - The incidence of endometrial hyperplasia, per FDA guidance, was planned to be ≤1% with an upper bound of the one-sided 95% CI <4%
  - Biopsies were centrally and sequentially read by 3 independent pathologists
  - Endometrial hyperplasia was diagnosed with a consensus of 2 of 3 pathologists
    - Additional findings such as polyps were also reported
  - Endometrial safety population was analyzed (women with an acceptable biopsy at baseline, and a biopsy at 12 months or endometrial hyperplasia prior to month 12)
- Secondary safety endpoints related to endometrial bleeding were analyzed in the safety population and included
  - Proportion of women with cumulative amenorrhea (defined as no bleeding or spotting) over 12 months
  - No bleeding (% by trimester and cumulative for 28-day cycles)
  - Number of days with bleeding and/or spotting

Results

Participant Disposition and Demographics

- Of the 1845 women randomized to treatment, 1835 received at least 1 capsule (safety population), and 1275 completed the study (**Figure 1**)
  - Most common reasons for study discontinuation were adverse events (AEs; 8.9%), subject withdrawal (8.2%) and lost to follow-up (7.5%)
  - 1255 women were included in the endometrial safety population
- Women had a mean age of 55 years and mean BMI of 27 kg/m²; 65% of the women were white and 32% were black (**Table 3**)

Figure 1. Disposition of REPLENISH participants



Population, n (%)	1.0 mg E2 / 100 mg P4	0.5 mg E2 / 100 mg P4	0.5 mg E2 / 50 mg P4	0.25 mg E2 / 50 mg P4	Placebo
Safety	415	424	421	424	151
Completed at 52 weeks	284 (68.4)	305 (71.9)	312 (74.1)	281 (66.3)	93 (61.6)
Discontinued	131 (31.6)	119 (28.1)	109 (25.9)	143 (33.7)	58 (38.4)
Adverse event	46 (11.1)	33 (7.8)	34 (8.1)	41 (9.7)	10 (6.6)
Lost to follow-up	27 (6.5)	30 (7.1)	26 (6.2)	38 (9.0)	17 (11.3)
Subject withdrawal	36 (8.7)	42 (9.9)	29 (6.9)	31 (7.3)	13 (8.6)
Other*	22 (5.3)	14 (3.3)	20 (4.8)	33 (7.8)	18 (11.9)
Endometrial Safety	280	303	306	274	92

*Other included investigator decision, lack of efficacy, protocol deviation and other.

Table 3. Demographics of REPLENISH participants (safety population)

Treatment	Estradiol / Progesterone				Placebo
	1 mg / 100 mg	0.5 mg / 100 mg	0.5 mg / 50 mg	0.25 mg / 50 mg	
n	415	424	421	424	151
Age, y Mean ± SD	54.7 ± 4.4	54.5 ± 4.5	54.9 ± 4.3	54.4 ± 4.0	54.5 ± 4.3
Race, n (%) White Black Other*	 271 (65) 134 (32) 10 (2)	 281 (66) 136 (32) 7 (2)	 276 (66) 133 (32) 12 (3)	 273 (64) 140 (33) 11 (3)	 100 (66) 46 (31) 5 (3)
BMI, kg/m² Mean ± SD	26.8 ± 4.1	26.7 ± 4.3	26.7 ± 4.0	26.7 ± 4.0	26.6 ± 3.9

*Other included Asian, American Indian, Alaska Native, Native Hawaiian, Pacific Islander, Unknown, or other

Endometrial Safety Endpoints

- Endometrial hyperplasia incidence for all treatments was 0% (**Table 4**)
  - No endometrial cancer was found
- Active and disordered proliferation at 12 months ranged from 0.3% to 2.9% with TX-001HR (**Table 4**)
- Endometrial polyp incidence at 12 months ranged from 1.4% to 3.3% with TX-001HR (**Table 4**)

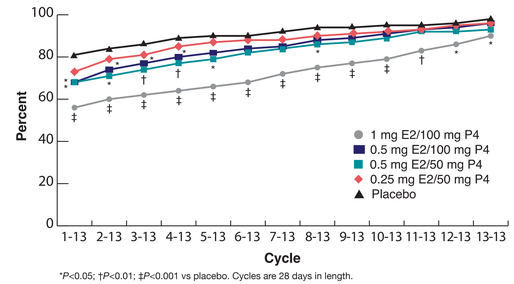
Table 4. Endometrial safety endpoints at 12 months (endometrial safety population)

Treatment, n (%)	Estradiol / Progesterone				Placebo
	1 mg / 100 mg	0.5 mg / 100 mg	0.5 mg / 50 mg	0.25 mg / 50 mg	
n	280	303	306	274	92
Hyperplasia at 12 months Incidence rate 1-sided upper 95% CI	 0 (0) 1.06%	 0 (0) 0.98%	 0 (0) 0.97%	 0 (0) 1.09%	 0 (0) 3.20%
Proliferative endometrium Screening Month 12	 2 (0.7) 8 (2.9)	 5 (1.7) 5 (1.7)	 2 (0.7) 1 (0.3)	 1 (0.4) 3 (1.1)	 0 (0) 0 (0)
Endometrial polyps Screening Month 12	 5 (1.8) 4 (1.4)	 7 (2.3) 6 (2.0)	 5 (1.6) 10 (3.3)	 5 (1.8) 7 (2.6)	 0 (0) 0 (0)

Bleeding and Spotting Incidence (safety population)

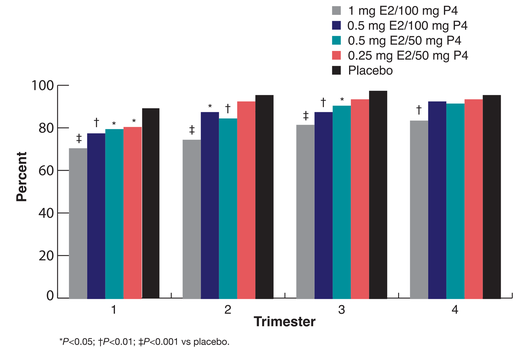
- Cumulative amenorrhea from cycle 1 to 13 was observed in 56% to 73% of women for E2/P4 doses versus 79% for placebo, and was >90% in cycle 13 (**Figure 2A**)
- Percentages of women with amenorrhea ranged from 70% to 80% with TX-001HR versus 89% with placebo in trimester 1 and increased to 83% to 93% versus 95%, respectively, in trimester 4 (**Figure 2B**)
- Bleeding and/or spotting days tended to decrease throughout the study

Figure 2A. Cumulative Amenorrhea (No Bleeding or Spotting) to Cycle 13



*P<0.05; †P<0.01; ‡P<0.001 vs placebo. Cycles are 28 days in length.

Figure 2B. Amenorrhea (No Bleeding or Spotting) per Trimester



*P<0.05; †P<0.01; ‡P<0.001 vs placebo.

Conclusions

- This TX-001HR clinical trial provided evidence of endometrial safety
  - All TX-001HR doses had 0% incidence of endometrial hyperplasia, achieving the ≤1% incidence (1-sided, upper 95% CI <4%) as per FDA guidance
  - No endometrial malignancies were found
- The absence of endometrial hyperplasia and endometrial cancer in this study should be considered in light of case reports of endometrial hyperplasia and endometrial cancer observed with CBHT[4-6]
  - Endometrial safety observed with TX-001HR underscores the need for CBHT safety studies given their potential risks
- If approved, TX-001HR may be an appropriate alternative combination HT with E2/P4 for treating VMS, especially in the estimated millions of postmenopausal women currently using less regulated and unapproved CBHT

Disclosures

- DFA (within the past 3 years) has received research support from Actavis, Bayer Healthcare, Endoceutics, Glenmark, Merck, Radius Health, Shionogi Inc, and TherapeuticsMD; and has served as a consultant to Abbvie, Actavis, Agile Therapeutics, Bayer Healthcare, Endoceutics, Exeltis, InnovaGyn, Merck, Pfizer, Radius Health, Sermonix Pharmaceuticals, Shionogi, Inc, Teva Women's Healthcare, and TherapeuticsMD. RL has research grants from TherapeuticsMD and consults (within the past 3 years) for TherapeuticsMD, AMAG, JDS Therapeutics, Pfizer, Allergan, Teva and Mithra. RK has received research grants and support from Therapeutics MD (paid to Sutter Health), and has served as a consultant to Allergan, AMAG, Amgen, Azure, Heptares, Juniper, Merck, Noven Pharmaceuticals, Palatin, Pfizer, Shionogi, Sprout, and Valeant. GC consults to multiple pharmaceutical companies, including but not limited to TherapeuticsMD and has stock options with TherapeuticsMD. JP has received consultant fees from Wyeth/Pfizer, Shionogi Inc., Radius Health Inc, and TherapeuticsMD; and has stock options with TherapeuticsMD. GG, SG, BB and SM are employees of TherapeuticsMD. BB is also on the Board of TherapeuticsMD.
- TherapeuticsMD sponsored the study and supported the medical writing assistance provided by Dominique Verlaan, PhD (Precise Publications, LLC).

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